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Periodontitis and Schizophrenia: A Potential Bidirectional Link

Periodontal Disease Could Represent a Risk Factor for Schizophrenia and Schizophrenia is a Risk Factor for Periodontal Disease

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Abstract

Periodontitis is a chronic oral inflammatory disease caused by virulent subgingival bacteria stimulating the host's immune system, leading ultimately to tooth loss. Schizophrenia is a severe mental illness with a variety of negative, positive, and cognitive symptoms, which are hardly controlled by medication and that may have drastic consequences on the patients' social, academic, and professional spheres of life. Surprisingly, schizophrenia has often been reported to be affiliated with chronic inflammation in the CNS without pointing out any typical center of inflammation. This review aims to establish whether there is a bidirectional relationship between schizophrenia and periodontal disease and to elucidate its potential mechanisms. This is the first review exploring this relationship, although several reviews have been studying the link between periodontal disease and other mental disorders such as Alzheimer's disease. A total of 71 articles have been found on PubMed and 30 articles were retained and met our criteria. On one hand, our results show that periodontal disease could be a risk factor for schizophrenia because it induces systemic inflammation, which could affect the central nervous system's homeostasis. Systemic inflammation could trigger microglial activation, a phenomenon associated with schizophrenia. Matrix metalloproteases (MMPs) are directly involved in periodontal tissue and bone destruction and are upregulated and overexpressed in schizophrenia patients' fluids. We now know that there is a link between the intestinal microbiota and mental illness. It seems evident that the healthy and pathological oral microbiota, in the case of periodontal disease, can also play a role in mental health and schizophrenia. On the other hand, the opposite relationship presuming that schizophrenia could be a risk factor for periodontal disease is veracious and well-studied.

Periodontitis

Periodontitis is a chronic oral inflammatory disease affecting 20 to 50% of the global population and its prevalence increases with age.1 The disease causes the loss of periodontal ligament collagen fiber attachment and alveolar bone destruction, leading ultimately to tooth loss.**[**1**]** Periodontal disease is caused by an alteration in the microbiota, which shifts from a symbiotic microbial community to a dysbiotic one.**[**1**]** In fact, periodontitis is predominantly a bacterial infection: particular types of subgingival bacteria have been identified as virulent and are strongly associated with the pathogenesis of periodontal disease.**[**2**]** Biofilms causing gingivitis and periodontitis are site-specific, complex polymicrobial communities, and are resistant to antimicrobial agents and host-defense mechanisms.**[**2**]** The age at onset, severity and progression of the disease depend on the systemic risk factors of the host, for which reason only a subgroup of adults suffered from severe periodontitis in a study aiming to determine the prevalence of the disease in the United States population.**[**2**]**

Individual risk factors for periodontitis

Gender:

Men of all ages, race and ethnic groups, and geographic locations have significantly more periodontal disease than women, assessed by prevalence, extent and severity.**[**2**]**

Smoking:

Smoking cigarettes is a major risk factor for subsequent tooth loss. An association between necrotizing ulcerative gingivitis (NUG) and tobacco smoking was reported in 1947. Many studies have shown an association of cigarette smoking with periodontal measures. After adjustments for confounding factors, the Erie County study revealed that smoking is a major risk factor with odds ratios for moderate smoking of 4 to 5 both for periodontal attachment loss and alveolar crest bone loss. Grossi and colleagues illustrated that the prevalence of periodontal disease of greater severity increased with the number of pack-years smoked. Overall, these authors agreed that the amount of alveolar crest height loss was positively correlated with the number of pack-years of smoking. A systematic review by Patel et al. showed that smoking negatively affected bone regeneration after periodontal treatment. In the same vein, cigar and pipe smoking appeared to have the same effects on the periodontium as cigarette smoking. **[**2**]**

Cannabis use:

A systematic review and meta-analysis including four high-quality studies with a total of 13 491 subjects came to the conclusion that cannabis use is associated with higher prevalence of periodontitis regardless of tobacco use.**[**9**]**

Alcohol:

Alcohol consumption is associated in a dose-dependent manner with increased severity of clinical attachment loss. Odds ratio for the risk of attachment loss when 5, 10, 15, and 20 drinks are consumed per week were 1.22, 1.39, 1.54, and 1.67.2

Diabetes:

The severity of periodontitis is greater among diabetes patients. Those with uncontrolled diabetes have particularly more severe periodontal disease than individuals with no diabetes from the same population. A 2-year follow-up radiographic study of Prima Indians showed that poor glycemic control in type 2 diabetes patients was associated with higher alveolar bone loss and more severe progression of periodontal disease than among individuals without type 2 diabetes. In addition, prediabetes and gestational diabetes are also known as risk factors for periodontal disease.**[**2**]**

Obesity and metabolic syndrome:

Suvan et al. review of cross-sectional studies concluded that the odds ratio of developing periodontal disease in obese or overweight individuals is 2.13. Several studies agreed that the risk of developing periodontal disease increases with the body mass index. In a meta-analysis of 57 studies, odds ratio ranged from 1.88 to 4.40 after adjustment for age, gender, smoking, alcohol consumption and frequency of tooth brushing.**[**2**]**

Osteoporosis, dietary calcium, and vitamin D:

Nishida et al. reported that individuals, especially women, with a low intake of dietary calcium had more severe periodontal disease. Several studies showed that calcium and vitamin D supplement

consumption have beneficial effects on tooth retention. Another study demonstrated that the use of bisphosphonates, which are mainly used to treat osteoporosis, helped reduce alveolar bone loss in patients suffering from low bone mineral density. Nevertheless, this medication may lead to osteonecrosis of the jaw in 0.1% of cases, according to a meta-analysis.**[**2**]**

Stress:

Studies have shown that there is a correlation between chronic periodontal disease and the psychological stress status of individuals. Hugoson et al demonstrated that traumatic life events like the loss of a spouse increased the risk of periodontal disease, but the ability of individuals to cope with those stressful events reduced their potential of causing the progression of periodontal disease. Indeed, individuals with active coping strategies had milder periodontal disease than individuals with passive coping strategies.**[**2**]**

Genetic factors:

On one hand, Mariza and colleagues review of literature demonstrated that aggressive periodontitis is highly prevalent among certain families and it is inherited as an autosomal- dominant trait in black families. On the other hand, a study by Shearer et al. concluded that parents with poor periodontal health tend to have offspring with poor periodontal health, but this association did not distinguish genetic and environmental factors. Additionally, Laine et al found that gene polymorphism in the interleukin-1, interleukin-6, interleukin-10, vitamin D receptor, and CD-14 genes play a role in chronic periodontitis in specific populations.2 In the same perspective, Sanders et al. reported a significant association of a rare TSNAX-DISC1 noncoding RNA polymorphism with chronic periodontitis among a Hispanic population.**[**3**]** Hong et al revealed that the TENM2 locus is associated with chronic periodontitis whereas Divaris et al. pointed out its association with Aggregatibacter actinomycetemcomitans subgingival colonization levels in a North American sample. Ultimately, six genes were associated with periodontal disease: four (NIN, ABHD, WHAMM, and AP3B2) with severe chronic periodontitis and two (red complex-KCNK1 and Porphyromonas Gingivalis-DAB2IP) with high periodontal pathogen colonization.**[**3**]**

Bacterial risk factor:

The presence of P. Intermedia was correlated with attachment loss in a group of Navajo adolescents. Likewise, P. gingivalis and B. forsythus were associated with increased risk for attachment loss.**[**4**]**

Age:

Advanced age is a questionable risk factor for periodontitis since we do not know if the cumulative effects of the disease are responsible for the higher prevalence of periodontitis in older groups.**[**4**]**

Socioeconomic status:

Old data from the U.S. Public Health Service indicated a positive association between periodontal disease and low socioeconomic status. However, this association was rejected when a more recent study adjusted for oral hygiene and smoking.**[**4**]**

Systemic disease:

Some systemic diseases with a depressed number of neutrophils and decreased function such as neutropenia, Chediak-Higashi syndrome, Down's syndrome and Papillon-Lefevre syndrome were associated with severe periodontitis.**[**4**]**

Schizophrenia

Schizophrenia is a severe mental illness with a lifetime prevalence of approximately 0.7%.5 More than half of diagnosed patients confront long-term psychiatric issues and 20% among them suffer from chronic symptoms and disability.6 Unemployment rate in schizophrenic patients is sadly 80 to 90%. Life expectancy is shortened by 10 to 29 years.6 From a financial point of view, schizophrenia costs around 11.8 billion euros per year in England to cover health and social care expenses.**[**6**]** Symptoms of the disease include positive, negative symptoms, and cognitive symptoms.**[**5**]** Positive symptoms comprise of delusions, hallucinations and disorganization (thoughts disorders and bizarre behavior).**[**5**]** Negative symptoms involve affective flattening, paucity of thought or speech, lack of motivation, and emotional and social withdrawal.**[**5**]** Negative symptoms affect the ability of patients to undertake social relationships, to engage in activities, to live autonomously, and may even impair their work or study activities.**[**5**]** Cognitive impairment is responsible for poorer performance than control subjects in a range of cognitive functions.**[**6**]** Schizophrenia treatment is a combination of antipsychotic drugs

and psychological therapy, social support and rehabilitation.[6] Moreover, approximately two-thirds of patients continue experiencing positive symptoms two years after the start of antipsychotic medication and around one-third will continue experiencing these symptoms 6 years after establishing the diagnosis.[5] Additionally, different studies have shown that many patients continue experiencing negative symptoms even after controlling the positive symptoms.[5] Up to one-third of schizophrenia patients do not respond to medication at all.[16] Approximately 82% of patients relapse within 5 years after recovery from their first-episode psychosis and the majority of them relapse multiple times during the course of their disease.[16] The exact causes of the illness are still debated but a vulnerability-stress model interaction, suggested by Zubin and Spring 40 years ago, has been put forward to explain the physiopathology of schizophrenia.[11,16] In this model, genetic, epigenetic, and environmental factors supposedly result in brain abnormalities and abnormal responses throughout life upon exposure to relevant stressors.[16]

The diagnosis is established according to the criterions cited in the DSM-5. This latter describes a series of criterions A to F that must be met in order to diagnose schizophrenia. Criterion A addresses positive symptoms such as delusions, hallucination, disorganized speech, disorganized behavior and negative symptoms. Criterion B tackles the social and occupational dysfunction. Criterion C covers the required duration of symptoms, which is a 6-month minimum period with signs and persistent disturbance that must include at least one month of symptoms that meet criterion A. Criterion D excludes the main differential diagnoses which are schizoaffective disorders and depressive or bipolar disorders with psychotic features. Criterion E excludes the possibility that the symptoms are caused by substance use (drugs or medication) or a general medical condition. Criterion F excludes the differential diagnosis of global developmental delay or autism spectrum disorder.[7]

As cited above, the main differential diagnoses of schizophrenia are affective psychoses (bipolar disorder or major depressive disorder with psychotic features), other related non-affective psychoses (schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified), psychotic disorders induced by alcohol or other substances, and psychotic disorders caused by a general medical illness.[6]

Nevertheless, attenuated forms of auditory hallucinations and paranoid thinking occur in 5 to 8% of the healthy population, which may lead to the conclusions that current diagnosis methods might need enhancement.[6]

Individual risk factors of schizophrenia

Pregnancy, birth complications, and exposure to infectious agents:

Emergency caesarean section, bleeding during pregnancy, preeclampsia, and low birth weight are complications that increase the child's susceptibility of developing schizophrenia. Additionally, the use of forceps and low birth weight are associated with earlier age of onset of psychosis. The pathogenic mechanisms involved go as follows: foetal malnutrition, prematurity, hypoxic-ischemic events, and maternal infections during pregnancy or delivery.**[**8**]**

Inflammation of the mother:

Cohort studies revealed that mothers with increased markers of inflammation, particularly C-reactive protein and Interleukine-8 had offspring with higher risks of developing schizophrenia.**[**8**]**

Mother's age:

In one study, mothers aged younger than 19 and older than 40 were supposedly at higher risk of having offspring suffering from schizophrenia. Another cohort study showed that the risk decreased in offspring of mothers older than 30 years. Therefore, studies do not share the same conclusions.**[**8**]**

Advanced paternal age:

A paternal age of 34 years-old and higher has been associated with schizophrenia.**[**8**]**

Stress, trauma, social adversities, low social class, and isolation:

Epidemiological studies agree that stress and cortisol levels play a key role in the onset of psychosis. Higher levels of diurnal cortisol were observed in first-episode psychosis patients compared to control subjects or patients on antipsychotic treatment for less than 2 weeks.**[**8**]** Childhood adversity, defined

as sexual abuse, physical abuse, emotional or psychological abuse, neglect, parental death, and bullying was associated with increased risk of psychosis in adulthood, with an odds ratio of 2.78.**[**8**]** Furthermore, childhood trauma was found to be associated with the most severe form of symptomatology in adulthood.**[**8**]** A meta-analysis estimates a threefold increased odds of life events in a 3 month to a 3.6-year period prior to psychosis onset.**[**8**]** In addition, a low socioeconomic status, measured by paternal occupation, is purportedly associated with higher risks of psychosis, but studies diverge on this point. **[**8**]** Moreover, first-episode psychosis patients are more likely to live alone, to be single, to live in rental housing, to live in overcrowded conditions, to be unemployed, and to earn an income below official poverty, up to 5 years before the onset of psychosis.**[**8**]**

Migration:

Meta-analytics reviews have found that migrant populations are more at risk of developing psychotic disorders. Studies conducted in high-income countries including the UK, Germany, France, Italy and Canada show that refugees are more at risk of developing schizophrenia than non-refugee migrants. Surprisingly, the risk persists in the second and third generations.**[**8**]**

Urbanicity:

A meta-analysis conducted on 47 087 subjects with psychosis revealed a 2.39 odds ratio for psychosis in urban environments compared to rural ones. Furthermore, moving from a rural area to an urban area during childhood doubles the risks of developing schizophrenia and the more years the child spends in an urban environment, the higher the risk becomes.8 Living near or in a green space during childhood lowers the risks of developing schizophrenia in a dose-response association.**[**8**]**

Cognitive impairment and brain structural abnormalities:

Delayed developmental milestones in the first year of life, lower IQ in childhood, hearing impairment, emotional problems, and interpersonal difficulties early in life are reported in several patients with schizophrenia.**[**8**]**

Substance use:

Substance use is recognized as being prevalent in patients with schizophrenia. There is robust evidence that psychostimulants such as amphetamines and cocaine can induce psychosis. In fact, there is a two to threefold risk of developing schizophrenia with cannabis use and this risk increases in a dose-response relationship. There is stronger association when individuals start consuming cannabis earlier in their lives, use high-potency tetrahydrocannabinol (THC) cannabis or consume more frequently. Oddly, the age of onset of cannabis use correlates with the age of onset of psychosis. Lasting and continuous cannabis use weakens the prognosis, increases relapse rates and the duration of hospitalization and is associated with severe positive symptoms. Tobacco use and alcohol misuse have also been suggested as potential risk factors for schizophrenia, but further evidence is needed.**[**8**]**

Abnormalities of the immune system and neuroinflammation:

A meta-analysis indicates that some markers of inflammation (interleukin 6, tumor-necrosis factor, soluble interleukin 2 receptor, interleukin 1 receptor antagonist) increase in acute schizophrenia episodes and decrease during successful treatments. Strangely, individuals that experienced trauma during childhood have significantly elevated baseline peripheral inflammatory markers in adulthood.8

Genetic predisposition to schizophrenia

In a meta-analysis of genome-wide association study, 108 loci associated with schizophrenia were identified. They concerned dopamine synthesis, calcium channel regulation, immunity, and glutamate neuroreceptors. However, these associations may be the result of gene-environment interactions and epigenetics.**[**8**]** Genetic factors take part in the pathophysiology of schizophrenia, but their contribution is not exclusive.**[**7**]** Schizophrenia is associated with diminished fecundity, so alleles generating high risks are uncommon in the general population whereas alleles occasioning mild risks are more common since they are the result of balancing selection or genetic drift.**[**7**]** As a matter of fact, schizophrenia is highly polygenic and genome-wide association studies have suggested that more than a hundred distinct loci contribute to increase the risks of developing the disease.**[**7**]** Eleven rare and recurrent copy number variants have been demonstrated to considerably elevate the risks.**[**7**]** Sequencing studies have observed rare, inherited, and de-novo single-nucleotide polymorphisms, as well as insertion and deletion variants in schizophrenia.**[**7**]** Furthermore, genes associated with schizophrenia are very pleiotropic, meaning that they affect different phenotypic traits. **[**7**]** In fact, a study revealed a significant overlap of common risk variants between schizophrenia and bipolar disorder, between

schizophrenia and major depressive disorder, and to a lesser extent between schizophrenia and autism spectrum disorder.[7] Additionally, a large-scale genome-wide association study has evoked common variation at genes encoding glutamate receptors, the voltage-dependent calcium channel family of proteins, and dopamine receptor D2 in schizophrenia.[7] Genome-wide association studies have shown nonetheless that schizophrenia is most significantly associated with highly correlated variants in major histocompatibility complex (MHC).[7]

Association between microbiota and schizophrenia:

It is now established that there is a link between an alteration of the microbiota and many psychiatric disorders. Numerous scientific studies show that altered and modified gut microbiota is found in anxiety disorders, depression, epilepsy, and schizophrenia. It is now accepted that schizophrenic patients have a greater alteration of the intestinal barrier than the general population. The induction of a sick patient's gut microbiota into a healthy mouse causes the appearance of positive symptoms in the healthy mouse. Research has shown that people with schizophrenia have lower microbial diversity in their gut microbiota compared to healthy individuals, and that bacterial composition is also different. Moreover, certain types of bacteria seem to be more frequently associated with schizophrenia, while others are less abundant in people with this disease. Respect for the gut microbiota is now one of the key research avenues in schizophrenia, attempting to answer the main question: can dysbiosis predispose someone to schizophrenia, and what quantitative and qualitative alterations of microbiota composition underlie this phenomenon.

Common risk factors for periodontal disease and schizophrenia

In light of the above, common risk factors for schizophrenia and periodontal disease are higher markers of inflammation and inflammatory processes, tobacco smoking, alcohol consumption, cannabis use, stress, low social class and low socioeconomic status, genetic factors and dysbiosis.

Aim of this review

Environmental stressors are factors that alter homeostasis and engender a shift within the organism to restore optimal functioning. They consist of physiological stressors such as infectious agents and psychological/social stressors. [10] They impact the neuroinflammatory axis through actions in the periphery, by direct action on the central nervous system (CNS), or through alterations of the hypothalamic pituitary adrenal (HPA) axis. [10] As a result, neuroinflammation might provoke

symptoms like lethargy, anhedonia, anorexia, depression, cognitive dysfunction, and many signs of ‘’sickness behavior”.[10] In this review of literature, we are going to explore the possibility of periodontal disease being part of the etiological factors of schizophrenia through neuroinflammation mechanisms and other mechanisms. Next, we are going to determine whether patients with schizophrenia are more at risk of developing periodontal disease. Thus, the aim of this review is to establish if there is a bidirectional relationship between schizophrenia and periodontal disease and to elucidate its potential mechanisms. To the best of our knowledge, this is the first review exploring this potential relationship, although several reviews have been studying the link between periodontal disease and other mental disorders such as Alzheimer’s disease or depressive disorders.

Methodology

A total of 71 articles have been found on PubMed using the following keywords: ((periodontitis) OR (periodontal disease)) AND (neuroinflammation), ((periodontitis) OR (periodontal disease)) AND (schizophrenia), (schizophrenia) AND (neuroinflammation), schizophrenia, ((periodontitis) OR (periodontal disease)), ((neurodegenerative disease) OR (neuropsychiatric disorders)) AND ((inflammation) OR (neuroinflammation)). Articles that did not concern our main topic, articles in another language than English, and articles that focused on explaining the molecular changes in both diseases on human subjects and animals were excluded. Articles with human models were preferred.

Chronic periodontal disease could induce systemic inflammation

Altered subgingival microbiota has been linked with systemic inflammation.1 Ardila et al. showed that individuals with periodontitis present high levels of pro-inflammatory C-reactive protein (CRP) and leptin in their serum.1 As a matter of fact, bacteria could invade the tissue directly by secreting toxins, histolytic enzymes, and metabolic end-products. They could also invade tissues indirectly by stimulating the host’s immune system.1 For example, lipopolysaccharides (LPS) from P. Gingivalis induce the secretion of pro-inflammatory cytokines such as IL-1β, IL-8 and TNF-α.1 LPS from Aggregatibacter actinomycetemcomitans also provoke the production of pro-inflammatory cytokines such as IL-1, which is a major cytokine that directly activates osteoclast formation and activation, resulting in bone resorption.[1] In addition, neuropeptides like substance P (SP) are produced during inflammatory states and both SP and its receptor (NK-1R) are present in the junctional epithelium of the oral cavity.[1] Levels of SP in the gingival crevicular fluid and plasma correlate with the clinical

severity of periodontal disease.[1] Chronic periodontal disease could therefore provoke systemic inflammation.

Periodontal disease could affect the homeostasis of the central nervous system (CNS)

Around a thousand bacterial species are found in periodontal pockets.[1] Patients with chronic periodontitis primarily have gram-negative anaerobic bacteria in their subgingival sulcus, including Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola, which are part of the red complex.[1] Bacterial infection is necessary but not sufficient to provoke periodontal damages.[1] In fact, these bacteria can also be found in healthy gingival tissues.[1] As discussed above, periodontal disease is highly multifactorial and risk factors including genetic predisposition, stress, and other environmental factors enhance the chances of provoking a host-immune inflammatory response, leading to the secretion of inflammatory mediators (Il-1, IL-6, TNFα, PGE2) which activate MMPs production.[2,9,1] MMPs engender connective tissue degradation and bone resorption, which are clinically perceived by bleeding on probing, attachment loss and alveolar bone loss.[1]

Bacteria found in periodontal infections can affect the CNS through different routes and mechanisms. First, bacteria may intrude the bloodstream and directly infiltrate the brain.[1] Indeed, P. Gingivalis adheres to erythrocytes which serve as a transport vehicle and hide this bacterium from neutrophils and B cells, leading to systemic infection. [1] Secondly, bacteria may invade the CNS using the peripheral pathways.[1] In fact, oral Treponema has been found in the trigeminal ganglia and in the brainstem and cortex of human subjects.[1] Thirdly, bacteria can indirectly affect the CNS through systemic immune activation and neuroinflammation.[1] A local immune response in the brain parenchyma can be induced by peripheral cytokines attaining the brain.[1] Cytokines enter the brain either by crossing the blood-brain-barrier (BBB) or by increasing its permeability, by accessing areas that are deprived of BBB such as the circumventricular organs and the choroid plexus regions, or by penetrating the perivascular regions.[1] CNS invasion results in the activation of astrocytes and microglia, increased permeability of the BBB, and the excessive production of pro-inflammatory cytokines and cytotoxic molecules, giving rise to neuronal cell death and degeneration.[1]

Inflammation could play a role in schizophrenia

Schizophrenia has often been reported to be affiliated to chronic inflammation in the CNS without pointing out any typical center of inflammation.[11] Strangely, symptoms of schizophrenia have been recalled in several infectious diseases (encephalitis, HSV-1, HSV-2, and measles) and auto-immune diseases (scleroderma and system lupus erythematosus).[11] In a study conducted on 31 patients with schizophrenia and 30 control individuals, patients with schizophrenia had higher titers of various pathogens (cytomegalovirus, herpes simplex virus, Epstein-Barr virus, mycoplasma, chlamydia and toxoplasma) than healthy controls.[12] A study showed that mean and median serum levels of maternal IL-8 during the second or third trimester of pregnancy were nearly twice as high in the mothers of offspring that developed schizophrenia spectrum disorders in adulthood than in the mothers of other subjects.[13] Also, Il-6 levels in childhood predict the later risk of schizophrenia, and cytokines and C-reactive protein in childhood increase the later risk for schizophrenia.[11]

Studies have revealed a reduction in CNS volume in the first episode of schizophrenia that evolved during the course of the disease.[11] In a study comparing magnetic resonance imaging and genotype analysis of 44 right-handed male schizophrenic patients to those of 48 right-handed healthy male subjects that had about the same age and educational achievements, patients carrying Interleukin-1β–511 allele 2 polymorphism, which is associated with enhanced interleukin-1β production, showed bifrontal-temporal gray matter volume deficits and generalized white matter loss.[14] Maternal IL-8 levels have been correlated with loss of CNS volume as well.[11]

Schizophrenia patients have elevated inflammatory markers compared to healthy subjects

In a meta-analysis aiming to understand cytokine level variation in different phases of schizophrenia and other psychiatric diseases compared to healthy control subjects, first-episode schizophrenia patients had increased levels of IL-1RA alone after adjustments for in-between study heterogeneity.[17] In patients with acute exacerbation of chronic schizophrenia, effect sizes showed higher levels of IFN-γ, IL-1β, IL-6, IL-12, and sIL-2R when studies were calibrated for heterogeneity and small studies discarded.[17] In chronically ill patients with schizophrenia, there were small to medium effect sizes for elevated sIL-2R only when in-between study heterogeneity was taken into account and small studies were ruled out.[17] In the discussion of this meta-analysis, authors found it intriguing that all of the cytokines that were elevated in acutely ill patients with schizophrenia and other psychiatric disorders were modulated through the nuclear factor-κB, signaling pathway that is commonly activated in inflammatory and autoimmune disease.[17]

Inflammation and microglial activation play a role in schizophrenia

Microglia are highly plastic cells that can modulate their behavior and morphology depending on environmental changes.[16] They have a crucial role in synaptic pruning during brain development and in adulthood.[16] They improve synaptic communication and help organizing the neuronal network.[16] They are also implicated in neuroplasticity, which is the ability of the brain to adjust its neuronal connections and to adapt to environmental changes.[16] Microglia are involved in neuronal degeneration when they are activated and when they adopt certain phenotypes.[16] In fact, systemic infections trigger a series of metabolic and humoral pathways that communicate with the brain.[16] Metabolic and behavioral changes in the CNS are normally adaptive, but they could become maladaptive if microglia have been primed by an ongoing pathology, neuroinflammation, or stress.[11,16] In these cases, microglia switch their phenotype to an aggressive pro-inflammatory state, in which pro-inflammatory cytokines affect neurotransmitter function, potentially leading to a psychotic episode.16 In post-mortem brain tissue of schizophrenia patients, an association between microglial activation and schizophrenia had been remarked, especially in the white matter regions. In a large meta-analysis about neuroinflammation in post-mortem schizophrenic brains, 22 articles studied microglial markers. Out of the 22 articles, 11 studies declared increased microglial markers in schizophrenia patients' post-mortem brains, whereas 8 studies hadn't noted any effect and 3 studies reported decreased microglial markers.[16] In a series of meta-analyses by Miller et al., patients with acute schizophrenia episodes had alterations in cytokines, chemokines, lymphocytes, and oxidative stress markers in their blood and these alterations normalize with antipsychotic medication, contrary to other markers that remain elevated throughout the disease course.[16] In the same meta-analysis, patients infected with Toxoplasma Gondii and with elevated IgM titers, which are markers of acute recent infection or persistent infection, were linked to acute psychotic exacerbations.[16] In a meta-analysis written by Wang et al. and based on 16 studies, several alterations in the cephalo-spinal fluid were similar to those reported in the peripheral blood.[16] Nevertheless, these results shouldn't be taken at face value due to their lack of homogeneity and cofounding factors. Notably, Miller et al. recognized race, body mass index, and smoking as confounding factors that were not taken into consideration.[16] To sum up, psychoneuroimmunology research hypothesizes that neuroinflammation could generate primed microglia which have a hand in altered neuroplasticity, leading to structural and chemical abnormalities, and potentially triggering psychosis.[16]

The role of MMPs in periodontitis and schizophrenia

Matrix metalloproteases (MMPs) are a group of 23 endopeptidases19 that cleave the extra-cellular matrix (ECM) components.18 They are involved in mediating immune responses and contribute to neuroinflammation and physiological or pathological processes in the brain.18 MMPs also play a key role in pathological tissue destruction associated with periodontal disease.19 Among them, MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-11, MMP-12, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 and MMP-28 have been shown to be expressed in the brain.[18] Some of them are only expressed in the brain under specific physiological or pathological conditions.18 In a review studying the role of MMPs in periodontal disease, MMPs largely reported in the gingival crevicular fluid (GCF) are MMP-8, MMP-9, and MMP-13.[19] First, MMP-8 represents 80% of the collagenase found in the GCF and it assumes the role of the main collagenase leading to gingival and periodontal ligament collagen destruction.[19] Secondly, MMP-9 is the most influential proteinase involved in bone resorption.[19] In a comparative study, significantly higher salivary MMP-8 and crevicular MMP-9 levels were detected in patients with periodontitis compared to subjects with gingivitis and healthy controls.[19] MMP-3 and MMP-7 concentrations are also significantly increased in the GCF of patients with periodontitis.[19]

In regard to MMP-3, which is upregulated in periodontal disease, it disrupts the BBB, favors neuroinflammation, and is upregulated in many brain pathologies.[18] It encourages the synthesis of cytokines, promotes positive feedback for inflammatory response, and causes microglial activation.[18] As we have already explained, microglial activation is associated with schizophrenia. Thus, the increased concentrations of MMP-3 in periodontal disease could be partly responsible for the pathogenesis of schizophrenia.

Concerning MMP-9, it was agreed that it plays an important role in establishing synaptic connections during development, in promoting brain plasticity during adulthood, and in myelination and synaptic pruning.[20] It can be involved in regeneration and degeneration processes and its overexpression has been associated with neurodevelopmental disorders.[20] Its expression can be controlled by cytokines.[20] In a phenotype-based genetic association study of over 1000 schizophrenia patients and over 1000 healthy control subjects, patients who carried the C allele (CC/CT) on the MMP-9 rs20544 gene, which is recognized to induce lower MMP-9 activity at the synapse than the MMP-9 T variant, had more severe schizophrenia symptoms (measured with the positive and negative syndrome scale (PANSS) score) than TT carriers.[21] However, these gene variants were not found to increase the risk of developing schizophrenia in case-control analysis.[21] A study on 432 patients with schizophrenia

and 558 control subjects showed a higher frequency of the less active C allele in schizophrenia patients which could lead to diminished MMP-9 activity in the prefrontal cortex.[22] In a study on 103 schizophrenia patients, several MMP-9 variants showed a ''trend toward significance'' ($0.005 < p < 0.05$) for association with treatment outcome, which was measured with PANSS scores.[23] The most notable single nucleotide polymorphisms (SNPs) found was rs13925, which is potentially linked with reduced risk of developing treatment-refractory schizophrenia in the presence of the homozygote recessive genotype.[23] Moreover, Ali et al. reported that the levels of MMP-9 were upregulated in the serum of patients with schizophrenia.[18] Domenici et al. also noted increased levels of MMP-9 in plasma of patients with schizophrenia.[18] Chang SH and al. also agreed that MMP9 activity is raised in the blood of schizophrenia patients.[18] Finally, Kumarasinghe N. and al. found that MMP-9 levels were upregulated before starting the treatment, but that they were no longer significantly higher once the treatment was administreted.[18]

To sum up, MMPs play a crucial role in inducing tissue destruction in periodontal disease and some of them play important functions in the brain.[19] MMP-3 and MMP-9, in particular, are found to be upregulated in periodontitis and are somehow linked to schizophrenia. On the one hand, MMP-3 upregulation causes microglial activation, which is associated to schizophrenia. On the other hand, certain gene variants of MMP-9 were linked to more severe schizophrenia symptoms and MMP-9 was found to be elevated in schizophrenia patients' blood, plasma, and serum according to different studies. These findings may draw a path to demonstrate that periodontitis is a risk factor for schizophrenia. At the moment, only correlation and association relationships were established so we cannot claim a cause-and-effect relationship.

The potential role of neuroinflammation in cognitive impairment symptoms in schizophrenia patients

Research has demonstrated a correlation between increased peripheral inflammation and cognitive impairment associated with schizophrenia.24 In fact, an association between C-reactive protein (CRP) levels and diminished cognitive performance (attention, memory, and learning abilities) was revealed by Misiak et al.'s systemic review on schizophrenia and bipolar disorder patients.[24] Moreover, studies have reported a negative association between general cognitive function and serum concentration of IL-6, sTNF-R1, and IL-1ra in schizophrenia patients.[24] Additionally, higher peripheral IL-1β mRNA levels were linked to brain volume reduction and verbal fluency impairments in a subgroup of schizophrenia patients.[24] Finally, minocycline and other anti-inflammatory adds-on to antipsychotics were found to help with cognitive symptoms of schizophrenia.[24] The following

evidence tends to go along with peripheral inflammation, as of that coming from periodontopathogens, contributing to schizophrenia's cognitive symptoms.

Anti-inflammatory treatment could help in schizophrenia

Anti-inflammatory therapy has been found to help with schizophrenia in short-term studies.[11] A 6-week prospective, randomized, and double-blind study in patients with an acute exacerbation of schizophrenia analysed the efficiency of combining risperidone, an antipsychotic and celecoxib (NSAID) (n = 25) in comparison with combining risperidone and a placebo (n = 25).[11] Response to treatment was significantly improved in the celecoxib add-on group.[11] However, the samples were not large enough to provide undisputable conclusions. Data from this study was joined to data of a similar 6-week study, reaching a sample of 90 cases that was analysed.[11] This time, patients who had been ill for 2 years or less benefited from the addition of celecoxib while patients who had been suffering from the disease for a longer period of time did not stand out from the placebo add-on group.[11] A meta-analysis of eight studies supported these findings and deduced that anti-inflammatory drugs (celecoxib, ASA) significantly benefited first-episode schizophrenia patients but did not have a significant effect on patients with chronic schizophrenia, and that they helped inpatients but not outpatients.[11] In a 2014 review study of double blind randomized placebo-controlled trials by Sommer et al., aspirin and estrogens were found to have weak to moderate beneficial effects when added to antipsychotic medication, whereas adjunctive use of celecoxib, EPA/DHA fatty acids, davunetide, and minocycline did not show efficacy.[16] Minocycline is an antibiotic from the tetracycline family that crosses the BBB and inhibits microglial activation.[11] We previously pointed out that microglial activation causes more inflammation by releasing more pro-inflammatory cytokines.[1] In other double-blind, placebo-controlled add-on studies, minocycline addition in early course of treatment was found to have a beneficial effect on negative and cognitive symptoms.[11] Interestingly, a case report by Miyaoka and colleagues described how a patient with treatment-refractory psychosis went into a remission of 7 years or longer following a bone marrow treatment he received for his leukemia.[15] Even though a case study does not provide strong evidence to draw conclusions, it shows that there is potentially a robust link between immune abnormalities and schizophrenia.[15] Regrettably, studies currently found in the literature show heterogeneous results, do not include a very large sample of individuals and contain confounding factors. Further studies are needed to better understand the potential benefits of anti-inflammatory drugs on schizophrenia

patients, to select ideal cases for this add-on treatment, and to elucidate the efficiency of long-term anti-inflammatory treatment on schizophrenia patients.

The connection between microbiome and schizophrenia

Recent scientific studies seem to confirm that there is a link between neuroinflammation and the onset and expression of mental illnesses **[**31**]**. To understand the underlying pathophysiology, it is important to examine the events that can lead to this inflammatory state. The theory of a link between the gut microbiota and mental health is gaining more and more attention in the scientific community **[**32**]**. In some patients with schizophrenia, there is a lack of anti-inflammatory bacteria and an increase in certain pro-inflammatory bacteria **[**33**]**. Thus, there is a reciprocal communication between the central nervous system and the enteric nervous system, with variable neurotransmitter involvement and mediation depending on the intestinal microbiota. It is not possible to discuss the intestinal microbiota without considering the oral microbiota. With more than 100 million bacteria per milliliter of saliva, the oral cavity is an ecosystem in its own right that should not be ignored in new medical theories regarding the role of our microbiota in mental health **[**34**]**. The oral microbiota is rich in bacteria, viruses, fungi, and protozoa. Depending on the healthy or pathological state of the oral cavity, the microbiota changes, which naturally changes the secretion of pro- or anti-inflammatory molecules in the oral cavity and eventually at the systemic level. The oral microbiota is the second richest in our body, just behind the intestinal microbiota. It is now accepted that an alteration of this microbiota can have local and systemic repercussions (cardiovascular disease, pneumonia, premature birth)**[**35**]**. The pathophysiology underlying this phenomenon is not bacterial sepsis with a classical infectious process, but rather the inflammatory response that is responsible for the local and systemic complications of oral dysbiosis, mainly represented by periodontitis. Porphyromonas gingivalis is strongly suspected to be involved in the pathophysiology of Alzheimer's disease or pancreatic carcinogenesis. The local and then systemic inflammation caused by periodontal disease can have a repercussion on the central nervous system. Pro-inflammatory cytokines secreted by periodontal bacteria can cross the blood-brain barrier and cause neuroinflammation that may be responsible for psychiatric disorders **[**36**]**. More generally, the inflammatory and chronic nature of dysbiosis promotes the development of psychiatric disorders. A study by Fawzi et al.**[**37**]** found a higher amount of Porphyromonas gingivalis in the saliva of patients with schizophrenia compared to that of healthy patients. In addition, a linear correlation was found between the severity of the disease and the expression of its symptoms and the presence of a large amount of specific gingival bacteria. Although the gut-brain interaction in schizophrenia is not

a new concept, studies on the role of the gut microbiota in the etiology and management of this disease are still in their infancy.

Today, it is not possible to determine the implications of dysbiosis on the onset and expression of schizophrenia. It is important to note that it may be easier to act on the microbiota to stabilize the disease, and this path represents hope and the future of clinical research. It is also crucial to keep in mind that the oral microbiota should not be excluded from clinical considerations, as periodontitis is a dysbiosis that can be easily quantified and evaluated in the clinic.

a. A few conclusions from an animal study model on mice

In an experimental study on mice, mice that were injected with P.gingivalis-LPS had an upregulated expression of inflammatory cytokines compared to the control group.**[**25**]** The P.gingivalis-LPS group had spatial learning and memory impairment compared to the control group.**[**25**]** Activated microglia were observed in the P.gingivalis-LPS group and the E. coli-LPS group, whereas they were rarely observed in the control group.**[**25**]** Both the P.gingivalis-LPS group and the E. coli-LPS group had a higher number of activated astrocytes in the hippocampus and the cortex. **[**25**]**

In another experiment, chronic periodontitis was reproduced on mice by repeated oral application of P. Gingivalis 3 times a week during 22 weeks.**[**26**]** The mice were sacrificed and their brain tissue was analysed.**[**26**]** Immunofluorescence microscopy detected proteases secreted by the bacteria in the hippocampus of every mouse in the experimental group (n=9) and none in the control group (n=10).**[**26**]** Degenerating neurons were found in the hippocampus of the experimental group, whereas they were not identified in the control group. **[**26**]**

Thus, these results confirm on an animal model that the LPS of a periodontopathogen, P.Gingivalis, could lead to cognitive impairment and could activate microglia and astrocytes in the cortex and hippocampus.**[**25**]** P. Gingivalis proteases could be detected in mice with chronic periodontitis and the bacteria caused neuron degeneration the hippocampus area.**[**26**]** This evidence supports our argument that periodontitis could lead to microglial activation, neurodegeneration, and therefore to schizophrenia.

Is schizophrenia a risk factor for developing periodontitis?

A cohort study performed on 3610 patients newly diagnosed with schizophrenia, treated with antipsychotics for at least 3 months, and followed during a one-year period of time aimed to understand risk factors of periodontal disease in those patients.[27] Patients with HIV/AIDS, diabetes mellitus, chronic pulmonary disease, osteoporosis and alcoholism were excluded from the study in order to diminish potential confounding factors.[27] Adjustments for sex, age, geographical region, income level, concomitant medical prescriptions, 2-year history of periodontal disease, potentially associated risk factors and diagnosis date (index date) were applied by the authors.[27] 63.9% of the individuals without a 2-year past history of periodontal disease developed periodontal disease.[27] Compared with non-users, ORs of first-generation antipsychotics (FGA), secondary-generation antipsychotics (SGA), anticholinergics, and antihypertensives were respectively 1.89, 1.33, 1.24, and 1.91.[27] Thus, in the following study, exposure to FGA, SGA, anticholinergics, and antihypertensives were additional risk factors of periodontal disease most probably due to the hyposalivation effects of these drugs.[27] Another study was conducted in Malaysia on 543 patients with schizophrenia over a 5-month period in order to assess their periodontal health using the Community Periodontal Index of Treatment Needs (CPITN) Index.[28] Patients with first-episode schizophrenia, substance dependence, and other medical disorders or comorbid learning disabilities were excluded from the study.[28] Only 1% out of the 543-subject sample had healthy gums compared to 3.2% in the general Malaysian population.[28] With regard to edentulism, the mean number of permanent teeth per person was 15.5 compared to 22.9 in the general population. However, the loss of teeth is not necessarily caused by periodontal disease.[28] A cross-sectional study performed in Taiwan that used the community periodontal index revealed that 49.5% of psychiatric inpatients (schizophrenia: 61%, length of illness: approximately 6 years) had periodontal pockets and 90% of all of those inpatients had periodontal disease.29 When investigating habits of patients with schizophrenia, only 22.5% of the participants had visited the dentist within one year and 27% of patients had significant anxiety about undergoing dental care.29 Around half of the patients (49%) neglected tooth brushing, 37% of total patients ate snacks regularly, 42.5% of participants were regular smokers, and only 17.5% of patients agreed that regular dental check-ups were necessary for dental health.[29] In a cross-sectional epidemiological study on 250 patients diagnosed with schizophrenia, taking antipsychotic medication and having no history of other systemic illness, there was a moderate to significant correlation between duration of disease and gingival index ($p < 0.001$), between duration of disease and plaque index ($p < 0.001$), and between duration of disease and probing pocket depth ($p < 0.001$).[30] Accordingly, schizophrenia patients are at greater risk of developing periodontal disease and other dental diseases such as tooth decay than healthy individuals because of poor nutrition and oral hygiene, high consumption of snacks and sugary

drinks, high use of tobacco, alcohol, and psychostimulants, low number of visits to the dentist, financial barriers making it more difficult to access dental care, and use of antipsychotics and other drugs frequently leading to xerostomia, which is known to aggravate periodontal disease.[28,29]

Discussion

In light of what has been discussed, periodontal infections could represent a risk factor for schizophrenia in the following order of events. Periodontal pathogens could induce systemic inflammation either by invading the host's tissues directly or indirectly by stimulating the host's immune system. Bacteria can henceforth intrude the CNS either directly by crossing the BBB, indirectly using the peripheral routes or by activating the immune system. These events are supported by certain findings discussed in the present review. Notably, schizophrenia patients happen to have more elevated markers of inflammation in the various stages of the disease, and they also have more pathogens than healthy individuals. Moreover, increased inflammatory markers (IL-6) during childhood multiplicate the risks of developing schizophrenia in adulthood. Thereupon, bacteria from periodontal disease could affect the brain and occasion trigger microglial activation. Brains of schizophrenia patients were analyzed and showed evidence of microglial activation. Maladaptive changes that appear with microglial priming are responsible for altered neuroplasticity and chemical abnormalities, and they could also provoke psychosis.

In a similar vein, MMPs, which are at fault in causing periodontal tissue destruction, are involved in microglial activation and degeneration processes. We have explained that a study has noted that individuals with MMP-9 allele (C) that induced less activity at the synapse had more severe schizophrenia symptoms than individuals with the other allele (T). Studies have shown that patients with schizophrenia have higher levels and raised activity of MMP-9 than healthy individuals and that the levels of this enzyme almost dropped almost to normal during the schizophrenia treatment course. These findings link periodontal disease and schizophrenia. Strangely, anti-inflammatory drugs such as aspirin, celecoxib, and minocycline may help in improving the symptoms of schizophrenia, a finding that supports the inflammatory and neuroinflammatory etiology of schizophrenia. When chronic periodontitis was reproduced on mice, degenerating neurons were found in the hippocampus of the experimental group and they were not identified in the control group. Furthermore, injection of P. Gingivalis' LPS in mice of the experimental group activates microglia as opposed to those of the control group.

Unfortunately, the evidence that we were able to collect and that showed the possibility of periodontitis being part of the physiopathology of schizophrenia was association and correlation evidence. Therefore, while there are strong association proofs that support that link, further studies are needed to establish this relationship with certainty. Additionally, it is extremely difficult to conduct reliable clinical studies on this relationship because of the large number of common risk factors that must be controlled and that can generate bias.

With regard to the possibility of schizophrenia being a risk factor of periodontitis, this relationship is acknowledged in schizophrenia as well as in various other mental illnesses. Patients with schizophrenia are more prone to develop periodontal disease for many reasons. They tend to have poor oral hygiene, to consume more snacks, to visit less frequently the dentist, to consume tobacco, drugs, and alcohol, and to use medication that causes hyposalivation. For these reasons, it is imperative that the governments, dentists, periodontists, physicians, psychiatrists, nutritionists, nurses and other health care professionals raise awareness on the importance of oral hygiene, regular dental check-ups, and a balanced, low-sugar nutrition among patients with schizophrenia and their friends and family.

Conclusion

Common risk factors for both periodontal disease and schizophrenia are higher markers of inflammation, tobacco smoking, alcohol consumption, cannabis use, stress, low social class and low socioeconomic status, and genetic factors. They may represent bias factors when trying to answer our main question: Is there a bidirectional relationship between periodontal disease and schizophrenia?

Various pathways explained in this review point out that periodontal disease could be a risk factor for schizophrenia. Firstly, chronic periodontal disease causes systemic inflammation, and its bacteria could affect the central nervous system's homeostasis. Cytokines secreted during periodontal infections can invade the CNS using various pathways. Schizophrenia patients have higher titles of inflammatory markers. In particular, first-episode schizophrenia patients and those having an acute psychotic event have increased inflammatory markers than healthy control subjects. Schizophrenia patients showed grey and white matter volume deficits, associated with enhanced interleukin-1β production. Secondly, periodontal disease could trigger microglial activation and therefore provoke a psychotic episode. Microglia play a key role in synaptic communication, neuroplasticity, and neurodegeneration. When primed during an inflammatory state, an ongoing pathology or stress, they can provoke a psychotic episode. In post-mortem brain tissues, an association between schizophrenia

and microglial activation was found. Thirdly, MMPs are enzymes expressed in both periodontal disease and schizophrenia. They contribute to neuroinflammatory pathways as they are key enzymes in periodontal tissue destruction, particularly MMP-8, MMP9 and MMP-13. MMP-3 is upregulated in brain pathologies, promotes neuroinflammation and causes microglial activation, which is linked to schizophrenia. MMP-9 is involved in degeneration processes and is overexpressed in the plasma of schizophrenia patients. Some MMP-9 generic variants were associated with more severe schizophrenia symptoms. They may influence the response to schizophrenia's treatments and decrease once the treatment is started. Fourthly, the use of anti-inflammatory therapy such as minocycline as an add-on to antipsychotics was found to help in cognitive symptoms in early course treatment. Celecoxib and ASA anti-inflammatory therapies as an add-on to antipsychotics enhanced response to treatment especially in early-course and first-episode schizophrenia. Other anti-inflammatory treatments discussed in this review were found helpful according to some studies. Finally, when P. Gingivalis-LPS was injected in mice, spatial and learning memory impairment and microglial activation were observed in the experimental group compared to the control group. When chronic periodontitis was reproduced in mice, degenerating neurons were found in the hippocampus of the experimental group. This evidence supports our argument that periodontitis could lead to microglial activation, neurodegeneration, and therefore to schizophrenia. Nevertheless, these arguments do not represent causality evidence and further clinical studies are needed to establish this link with certainty.

The opposite relationship stating that schizophrenia is a risk factor for periodontal disease is well-studied. Studies have shown that schizophrenia patients have generally less healthy gums, have more edentulism, and have a high prevalence of periodontal disease. Exposure to first and second-generation antipsychotics and anti-hypertensives, poor nutrition and oral hygiene, frequent sugary snacks, high substance use and low frequency of dental visits put them at elevated risk for periodontal disease.

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